

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5, 6, 14, 16-20 and 26-36 are pending in the application, with claims 1, 16, 26 and 32 being the independent claims. Claims 1 and 16 have been amended to more particularly point out and claim the invention. Claims 7, 15 and 21-25 have been withdrawn from consideration. New claims 26-36 have been added. Support for these new claims can be found in the specification, *inter alia*, for example, at page 7, lines 19-21 of the specification. The new claims are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Examiner's Interview

Applicants thank Examiner Meller and Supervisory Examiner Brumback for the courteous and helpful interview extended to Applicants' representatives Lawrence Bugaisky and Teresa Colella on March 17, 2004. As required from the Interview Summary sheet, Applicants are now presenting for the record their understanding of the substance of the interview.

Applicants discussed enablement. It is believed, as previously stated in the Office Action of November 19, 2003, that the specification has support for "A method of

treatment of metastasis of cancer cells...." The Examiner tentatively agreed that an amendment reciting this language should overcome the rejection.

Applicants also discussed all of the art, including Iwasaki, Y., *et al.*, *Jpn. J. Cancer Chemother.* 25:1412-1415 (1998) [hereinafter "Iwasaki *et al.* (1998)"]; Carter, R., *et al.*, *Br. J. Cancer* 65:37-39 (1992) [hereinafter "Carter *et al.*"]; Ohigashi, H., *et al.*, *Hepato-Gastroenterology* 43:338-345 (1996) [hereinafter "Ohigashi *et al.*"]; Kitamura, M., *et al.*, *Jpn. J. Cancer Chemother.* 17:1657-1660 (1990) [hereinafter "Kitamura *et al.*"]; Tsuji, Y., *et al.*, *Jpn. J. Cancer Chemother.* 23:1617-1620 (1996) [hereinafter "Tsuji *et al.*"]; Yamaue, H., *et al.*, *Arch. Jpn. Chir.* 59:302-309 (1990) [hereinafter "Yamaue *et al.*"]; Iwasaki, Y., *et al.*, *Jpn. J. Cancer Chemother.* 11:1674-1678 (1995) [hereinafter "Iwasaki *et al.* (1995)"]; and Takahashi, N., *et al.*, *J. Of Japan Surgical Society* 92:775-784 (1991) [hereinafter "Takahashi *et al.*"]. Applicants pointed out that none of the art discloses using ATII alone and that nowhere in the cited art is there the suggestion of using angiotensin alone without an additional chemotherapeutic. Examiner agreed to study this matter in more detail.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1-3, 5, 6, 14 and 16-20 under 35 U.S.C. § 112, first paragraph, because the claims allegedly "[contain] subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (Paper No. 3, page 2.) Applicants respectfully traverse the Examiner's rejection.

In regards to claims 1-3, 5, 6, 14 and 16-20, the Examiner has stated that "'[a] method of preventing metastasis of cancer cells' is not enabled by the instant

specification." (Paper No. 3, page 2.) However, the Examiner has also stated that "The specification does have support for treating metastasis of cancer cells..." (Paper No.3, pages 2-3). Applicants disagree that claims 1-3, 5, 6, 14 and 16-20 lack enablement. In response to the Examiner's statement, however, claims 1 and 16 have been amended to recite "A method of treatment of metastasis of cancer cells...". This amendment has been made solely to expedite allowance of the claims and not in acquiescence to the Examiner's rejection. This amendment renders moot the Examiner's rejection and places the claims in condition for allowance. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1-3, 5, 6, 14 and 16-20 under 35 U.S.C. § 102(b) as allegedly being anticipated by Iwaski *et al.* (1998); Carter *et al.*; Ohigashi *et al.*; Kitamura *et al.*; Tsuji *et al.*; Yamaue *et al.*; Iwaski *et al.* (1995); or Takahashi *et al.*. Applicants respectfully traverse this rejection, reiterate and incorporate by reference the arguments made in the Reply previously filed March 19, 2002.

The claimed invention is directed, *inter alia*, to the use of angiotensin-II without an additional chemotherapeutic agent 1) to treat metastasis in cancer (*e.g.* claim 1) and 2) to reduce the invasiveness of cancer cells (*e.g.* new independent claim 26).

The Examiner has argued that the Applicants' specification does not provide support for the use of angiotensin alone, stating "Nowhere in applicant's citations from the specification did it ever support the use of angiotension [sic] only as applicant contends. In fact, the specification makes it clear that other active agents along with the angiotension [sic] are contemplated for use, see page 11." (Paper No. 3, page 3).

Applicants respectfully disagree. The Applicants' specification states that the pharmaceutical compositions of the present invention "...*may* also contain therapeutically active agents in addition to the substance of the present invention." (*See*, Specification, page 11, lines 2-4, emphasis added). However, the inclusion of other chemotherapeutic agents is merely one embodiment of the present invention. Merely because certain embodiments of the invention "may" contain additional agents does not mean that all embodiments do so.

Contrary to the Examiner's arguments, there is support in the Applicants' specification for the use of angiotensin alone. For example, in Example 3: Effect of Angiotensin-II on breast cell cancer invasion, Applicants demonstrate that the treatment of cancer cells with angiotensin II significantly inhibits invasiveness (*see*, Specification, page 23, line 25 through page 24, line 7). Furthermore, in Example 4: Studies of effect of Angiotensin-II on breast cancer cell growth in culture, Applicants demonstrate that the cells grown in the presence of angiotensin II produce larger clusters, which is presumably due to increased cell-cell adhesion (*see*, Specification page 23, line 25 through page 24, line 14). None of these examples contain a chemotherapeutic agent in addition to angiotensin. Therefore, there is clearly support in the Applicants' specification for the use of angiotensin alone to treat metastasis in cancer and/or to reduce the invasiveness of cancer cells without an additional chemotherapeutic agent.

This is in contrast to the cited art that discusses the *co-administration* of angiotensin with anti-neoplastic drugs where, as indicated by the authors, angiotensin was most likely used to increase blood flow to the tumor thus aiding passage of the anti-neoplastic agent (*e.g.* methotrexate 5-FU, MMC, ACNU, CDNP etc.) to the tumor (*See*, for example Iwaski *et al.* (1995), English translation, page 7, lines 13-16;

Takahashi *et al.*, English translation, page 19, lines 18-21; Tsuji *et al.*, English translation, page 4, lines 4-11). Nothing in the cited art suggests the use of angiotensin *on its own* to treat metastasis of cancer cells and/or to reduce the invasiveness of cancer cells.

The Examiner states that Yamaue *et al.* and Iwasaki *et al.*, (1995) "...are both very explicit about using only angiotensin" and points to Yamaue *et al.* at page 303, number 2 and to Iwasaki *et al.* (1995) at page 1678 to support his argument. (See Paper No. 3, page 3). Applicants respectfully disagree and are unable to find any disclosure in Yamaue *et al.* and Iwasaki *et al.*, (1995) where angiotensin II is used alone.

At the exact location cited by the Examiner, Yamaue *et al.* states that "[t]he anticancer agents were then given by intravenous bolus injection through the opposite arm from the ATII." (See Yamaue *et al.*, page 303, number 2, lines 5-6). Therefore, Yamaue *et al.* do not use angiotensin alone. Furthermore, Iwasaki *et al.* (1995) states that the course of therapy *included* 5-FU, leucovorin, and MMC (See English translation, page 4, lines 4-11). Therefore, Iwasaki *et al.* (1995) do not use angiotensin alone. In summary, neither Yamaue *et al.* nor Iwasaki *et al.*, (1995) use angiotensin alone and it is new and surprising that angiotensin-II *on its own*, without an additional chemotherapeutic agent, has an effect on metastasis and cancer cell invasiveness. If the Examiner maintains this rejection, he is respectfully requested to indicate the specific citation that supports the rejection.

Thus, as also discussed at the Examiner's Interview, the claims are not anticipated by Iwasaki *et al.* (1995), Iwasaki *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Kitamura *et al.*, Tsuji *et al.*, Yamaue *et al.* and Takahashi *et al.*. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1-3, 5, 6, 14 and 16-20 under 35 U.S.C. § 103(a) as allegedly being obvious over Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Tsuji *et al.* or Iwaski *et al.* (1995) in view of Takahashi *et al.*, Kitamura *et al.*, or Yamaue *et al.*. Applicants respectfully traverse the rejection.

As argued above, the cited documents neither disclose nor suggest the use of angiotensin to treat metastasis in cancer and/or to reduce the invasiveness of cancer cells without an additional chemotherapeutic agent. In the cited documents, the effect of angiotensin on blood flow is utilized to control the blood flow to the tumor and a chemotherapeutic drug is given in combination with angiotensin to diminish the tumor size. In the cited documents, angiotensin is not used alone, but rather in combination with other drugs as an adjuvant to chemotherapy. Furthermore, nowhere in the cited art is there the suggestion of eliminating the other drugs and using angiotensin alone. In contrast, the specification clearly describes the use of angiotensin without an additional chemotherapeutic agent to treat metastasis in cancer and to reduce the invasiveness of cancer cells. (*See* arguments above at page 9, paragraph 1).

Thus, as also discussed at the Examiner's Interview, Applicants assert that the claims are not obvious over Iwaski *et al.* (1998), Carter *et al.*, Ohigashi *et al.*, Tsuji *et al.* or Iwaski *et al.* (1995) in view of Takahashi *et al.*, Kitamura *et al.*, or Yamaue *et al.*. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner has also rejected claims 1-3, 5, 6, 14 and 16-20 under 35 U.S.C. §103(a) as allegedly being obvious over Takahashi *et al.*, Kitamura *et al.*, or Yamaue *et al.*. Applicants respectfully traverse the rejection.

As argued above, the cited documents, including Iwaski *et al.* (1995) and Yamaue *et al.*, neither disclose nor suggest the use of angiotensin to treat metastasis in cancer and/or to reduce the invasiveness of cancer cells without an additional chemotherapeutic agent. Furthermore, nowhere in the cited art is there the suggestion of eliminating the other drugs and using angiotensin alone. In contrast, the specification clearly describes the use of angiotensin without an additional chemotherapeutic agent to treat metastasis in cancer and to reduce the invasiveness of cancer cells. (*See arguments above*).

Thus, as also discussed at the Examiner's Interview, Applicants assert that the claims are not obvious over Takahashi *et al.*, Kitamura *et al.*, or Yamaue *et al.*. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

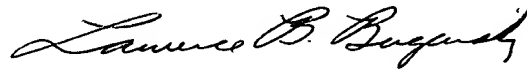
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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